

Individual Safety Report



3580351-3-00-01

 RES. INST. USA
 use by user-facilities,
 and manufacturers for
 ADULTORY reporting

Approved by FDA on 09/25/00

Mfr report #
PRIUSA2000009848

UP/Dist report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 3

A. Patient information			
1. Patient identifier ? - ?	2. Age at time of event: 47 yr or Date of birth: ??/??/??	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight UNK lbs or UNK kgs
In confidence			
B. Adverse event or product problem			
1. <input checked="" type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)			
2. Outcomes attributed to adverse event (check all that apply)			
<input type="checkbox"/> death (mortality) <input type="checkbox"/> life-threatening <input checked="" type="checkbox"/> hospitalization - initial or prolonged <input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage <input type="checkbox"/> other:			
3. Date of event (mo/day/yr) ??/??/??	4. Date of this report (mo/day/yr) 09/20/00		
5. Describe event or problem			
Report received by McNeil Consumer Healthcare: abstract #161 from the 2000 north American Congress of Clinical Toxicology Annual Meeting of severe APAP hepatic and renal toxicity following post operative therapeutic doses. According to the abstract, a 47-year-old man presented with congestive heart failure. A myocardial infarction was ruled out, but the patient had hepatic injury (ALT=94 IU/L, LDH=1611 IU/L). The patient's social history included 6 to 8 beers daily and smoking. On day 4, CABPG was performed. The patient was not fed, but was started on iron sulfate 325 mg three times daily. Post-operative medications included propoxyphene 100 mg/APAP 650 mg, APAP 325 mg/oxycodone 5 mg and APAP 325 mg/codeine 30 mg for pain and APAP 650 mg prn fever. Daily post-op APAP was 2.6g, 3.9g, 3.9g, 3.9g and 1.3g on post-op day 5. The patient received a total of 15.6g. On post-op day 5, hypotension and disorientation developed. ALT/AST were 2613 U/L and 4838 U/L. Lactic acidosis, hypoglycemia, pancreatitis, renal insufficiency, and thrombocytopenia followed. APAP level 8 hours after the last (Cont.)			
6. Relevant tests/laboratory data, including dates			
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			
Alcohol use, Smoking History of hepatic injury; 6 to 8 beers daily and smoking; CABPG			

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)		3. Therapy dates (if unknown, give duration) (from to (or best estimate))
#1 TYLENOL WITH CODEINE (unspecified) (ACETAMINOPHEN -		#1 ??/??/??
#2 PROPOXYPHENE (DEXTROPROPOXYPHENE) (Cont.)		#2 ??/??/??
2. Dose, frequency & route used		
#1 650 mg, prn, oral		
#2 100 mg, oral		
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced
#1 POST-SURGICAL TREATMENT		#1 <input checked="" type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
#2 PAIN		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1	#1	#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
#2	#2	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
9. NDC # - for product problems only (if known)		
10. Concomitant medical products and therapy dates (exclude treatment of event)		
No Concomitant Products Used		

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)		2. Phone number
R.W. JOHNSON PHARM. RES. INST. USA DIV. OF ORTHO PHARMACEUTICAL CORP. 920 U.S. Route 202 P.O. Box 300 Raritan NJ 08869 USA (Informing Unit)		908-704-4504
4. Date received by manufacturer (mo/day/yr) 09/15/00		3. Report source (check all that apply)
5. (A) NDA # 85-055		<input type="checkbox"/> foreign <input type="checkbox"/> study <input checked="" type="checkbox"/> literature <input type="checkbox"/> consumer <input checked="" type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
6. If IND, protocol #	IND #	
	PLA #	
7. Type of report (check all that apply)	pre-1938 <input type="checkbox"/> yes	
<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input checked="" type="checkbox"/> Initial <input type="checkbox"/> follow-up #	OTC product <input type="checkbox"/> yes	
8. Adverse event term(s)		
1) HEPATOCELLULAR DAMAGE		
2) HYPOTENSION		
3) HYPOGLYCAEMIA		
4) THROMBOCYTOPENIA		
5) RENAL FUNCTION ABNORMAL		
6) ACIDOSIS LACTIC		
7) PANCREATITIS (Cont.)		
9. Mfr. report number PRIUSA2000009848		

E. Initial reporter

1. Name (last, first, middle initial) [REDACTED] DSS USA		2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation Unknown	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk
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Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

SEP 27 2000

Individual Safety Report



3580351-3-00-02

 RES. INST. USA
 use by user-facilities,
 and manufacturers for
 MANDATORY reporting

Approved by FDA on 09/15/95

 Mfr report #
 PRIUSA2000009848

UF/Dist report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 2 of 2

A. Patient information

1. Patient identifier	2. Age at time of event: or Date of birth:	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
In confidence			

B. Adverse event or product problem

1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)	
2. Outcomes attributed to adverse event (check all that apply)	
<input type="checkbox"/> death (mo/day/yr)	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
<input type="checkbox"/> other: _____	
3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #3 OXYCODONE (OXYCODONE)		3. Therapy dates (if unknown, give duration) (from/to or best estimate) #3 ??/??/??	
#4 APAP WITH CODEINE (PANADEINE CO)		#4 ??/??/??	
2. Dose, frequency & route used #3 5 mg, oral		5. Event abated after use stopped or dose reduced	
#4 30 mg, oral		#3 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
4. Diagnosis for use (indication) #3 PAIN		#4 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
#4 PAIN		8. Event reappeared after reintroduction	
6. Lot # (if known) #3 _____ #4 _____		#3 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
7. Exp. date (if known) #3 _____ #4 _____		#4 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
9. NDC # - for product problems only (if known)			
10. Concomitant medical products and therapy dates (exclude treatment of event)			

D. All manufacturers

1. Contact office - name/address (& mfring site for devices)		2. Phone number	
4. Date received by manufacturer (mo/day/yr)		3. Report source (check all that apply)	
		<input type="checkbox"/> foreign	
		<input type="checkbox"/> study	
6. If IND, protocol #		<input type="checkbox"/> literature	
7. Type of report (check all that apply)		<input type="checkbox"/> consumer	
<input type="checkbox"/> 5-day <input type="checkbox"/> 15-day		<input type="checkbox"/> health professional	
<input type="checkbox"/> 10-day <input type="checkbox"/> periodic		<input type="checkbox"/> user facility	
<input type="checkbox"/> Initial <input type="checkbox"/> follow-up # _____		<input type="checkbox"/> company representative	
9. Mfr. report number		<input type="checkbox"/> distributor	
		<input type="checkbox"/> other: _____	
5. (A) NDA # _____			
IND # _____			
PLA # _____			
pre-1938 <input type="checkbox"/> yes			
OTC product <input type="checkbox"/> yes			
8. Adverse event term(s)			

E. Initial reporter

1. Name, address & phone #		DSS	
		SEP 27 2000	
2. Health professional? <input type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk	

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

SEP 26 2000

Individual Safety Report



3580351-3-00-03

Raritan NJ 08869
USA

Continuation Sheet for FDA-3500A Form

Page 3 of 3

Mfr. report # : PRIUSA2000009848

Date of this report : 09/20/00

B. Adverse event or product problem

B.5 Describe event or problem (Cont...)

dose was 15 mcg/ml. All cultures were negative. Liver biopsy showed centrilobular necrosis. N-acetylcysteine was given for 17 doses. With aggressive supportive care this patient recovered.

C. Suspect medication (Cont...)

Seq No.

C.1 Suspect medication

: 1

: TYLENOL WITH CODEINE (unspecified) (ACETAMINOPHEN/CODEINE)

G. All manufacturers

8. Adverse event term(s)

8) HEPATIC CIRRHOSIS

Source of report (Literature):

Seq No.

Author

Journal title

Article title

: 1

: [REDACTED]
: [REDACTED]
: [REDACTED]
: [REDACTED]

DSS

SEP 27 2000

SEP 26 2000



3580351-3-00-04

569

160 SURVIVAL AFTER MASSIVE INGESTION OF ACETAMINOPHEN PRESENTING AS COMA AND METABOLIC ACIDOSIS.

Rusyniak D, Dribben W, Furbie B, Kirk M. *Indiana Polson Center, Indiana University School of Medicine, Clarian Health Partners, Indianapolis, IN*

Objective: We present an unusual clinical scenario associated with massive acetaminophen overdose that through aggressive supportive care resulted in a good outcome despite a complicated clinical course. **Case Report:** A previously healthy 26-year-old female presented 12 hours after ingesting approximately 125 grams of Extra-Strength Tylenol® comatose with a GCS of 3. Vital signs included temperature 35.6°C, SBP 60 mmHg, and HR 130/min. She was intubated, resuscitated with IV fluids and started on pressors. Initial laboratory data revealed marked metabolic acidosis (pH 6.7, bicarbonate 5 mmol/L), renal insufficiency (creatinine 1.8 mg/dL), mild hepatotoxicity (AST 121 U/L, total bilirubin 0.7 mg/dL), and mild coagulopathy (INR 1.38, platelets 80,000/mm³). A 12-hour acetaminophen level was 1,148 mcg/mL followed by an 18 hour level of 1328 mcg/mL. Workup for other causes of metabolic acidosis (salicylates, iron, toxic alcohols) was negative. Despite treatment with IV NAC, the patient developed fulminant hepatic failure and underwent a 12 week hospital course including: 3 weeks of ventilatory support, prolonged hypotension (10 days of norepinephrine, max 68 mcg/kg/min), CVVH for renal failure, episodes of complete heart block, pancreatitis with pseudocyst, sepsis and pneumonia, ARDS, upper GI bleed, tracheo-esophageal fistula, pleural hematoma, pancytopenia (treated with 27 units of PRBCs and 17 units of platelets), and coagulopathy requiring 20 units of FFP. She eventually recovered and was discharged home with a normal neurological outcome and normal hepatic function. **Conclusions:** Massive ingestions of acetaminophen can present as metabolic acidosis and coma before the onset of hepatic failure. Despite fulminant hepatic failure and criteria suggesting poor prognosis, patients can survive with aggressive supportive care and without liver transplantation.

161 SEVERE ACETAMINOPHEN HEPATIC AND RENAL TOXICITY FOLLOWING POSTOPERATIVE THERAPEUTIC DOSES.

Barkhart KK, Donovan JW. *The Pennsylvania State University, Hershey, PA*

Background: Acetaminophen (APAP) is used to help control pain postop. We describe a patient who had multiple APAP orders with the potential to receive excessive in-hospital APAP. Our patient received ≤ 3.9 g/d (total 15.6 g) and developed severe hepatic and renal toxicity. **Case Report:** A 47-year-old male presented with CHF. A MI was ruled out, but there was hepatic injury, ALT 94 U/L, and LDH 1611 U/L. SH included 6-8 beers/d and smoking. On day 4, CABPG was performed. The patient was not fed, but was started on iron sulfate 325 mg TID. On postop day 5 hypotension and disorientation developed. ALT/AST were 2613 and 4838 U/L. Lactic acidosis, hypoglycemia, pancreatitis, renal insufficiency, and thrombocytopenia followed. Postop APAP orders included propoxyphene 100 mg/APAP 650 mg, APAP 325 mg/oxycodone 5mg, and APAP 325 mg/codeine 30 mg for pain, and APAP 650 mg prn fever. Daily postop APAP was 2.6 g, 3.9 g, 3.9 g, 3.9 g, and 1.3 g on postop day 5. An APAP level 8 hours after the last dose was 15 mcg/mL. All cultures returned negative, while a liver biopsy showed centrilobular necrosis. N-acetylcysteine was given for 17 doses. With aggressive supportive care this patient recovered. **Conclusions:** This case is a rare report where therapeutic APAP doses produced severe toxicity. This patient had risk factors, preceding hepatic injury, postop wound healing and fasting, heavy alcohol consumer, and the iron. Hospitals must develop protocols that prevent patients from receiving ≥ 4 g/d of APAP. Our pharmacy instituted the following changes. Warning flags are in the computer to alert pharmacists to check doses. No more than 3 prn doses are sent to patient floors. Finally, labels have been placed on all APAP products from the automated dispensing equipment that warn nurses to check the patient's total APAP dosing.

162 HEMOLYSIS FOLLOWING ACETAMINOPHEN OVERDOSE IN A PATIENT WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY.

Ruha AM, Sekden B, Brooks D. *Good Samaritan Regional Medical Center, Phoenix, AZ*

Background: Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency hemolyze when oxidant stress depletes reduced glutathione in erythrocytes. Therapeutic doses of many drugs precipitate hemolytic episodes in such patients, however, acetaminophen (APAP) is not considered one of them. We describe acute hemolysis following a large ingestion of (APAP) in a patient with unrecognized G6PD deficiency. **Case Report:** A 16-year-old African-American teenager, with previously undiagnosed G6PD deficiency, ingested an unknown amount of APAP, fluvoxamine, and clomipramine in a suicide attempt. A 6 hour APAP level was 680 mg/L. He received intravenous N-acetylcysteine

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